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CLINICAL REVIEW

Biomarkers associated with obstructive sleep apnea: A scoping review

Graziela De Luca Canto [a, b], Camila Pachêco-Pereira [b], Secil Aydinoz [c, d], Paul W. Major [b], Carlos Flores-Mir [b], David Gozal [d, e, *]

[a] Department of Dentistry, Federal University of Santa Catarina, Florianopolis, SC, Brazil
[b] School of Dentistry, Faculty of Medicine and Dentistry, University of Alberta, Canada
[c] GATA Haydarpasa Teaching Hospital, Istanbul, Turkey
[d] Department of Pediatrics, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, USA
[e] Comer Children's Hospital, USA

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SUMMARY

The overall validity of biomarkers in the diagnosis of obstructive sleep apnea (OSA) remains unclear. We conducted a scoping review to provide assessments of biomarkers characteristics in the context of obstructive sleep apnea (OSA) and to identify gaps in the literature. A scoping review of studies in humans without age restriction that evaluated the potential diagnostic value of biological markers (blood, exhaled breath condensate, salivary, and urinary) in the OSA diagnosis was undertaken. Retained articles were those focused on the identification of biomarkers in subjects with OSA, the latter being confirmed with a full overnight or home-based polysomnography (PSG). Search strategies for six different databases were developed. The methodology of selected studies was classified using an adaptation of the evidence quality criteria from the American Academy of Pediatrics. Additionally the biomarkers were classified according to their potential clinical application. We identified 572 relevant studies, of which 117 met the inclusion criteria. Eighty-two studies were conducted in adults, 34 studies involved children, and one study had a sample composed of both adults and children. Most of the studies evaluated blood biomarkers. Potential diagnostic biomarkers were found in nine pediatric studies and in 58 adults studies. Only nine studies reported sensitivity and specificity, which varied substantially from 43% to 100%, and from 45% to 100%, respectively. Studies in adults have focused on the investigation of IL-6, TNF-α and hsCRP. There was no specific biomarker that was tested by a majority of authors in pediatric studies, and combinatorial urine biomarker approaches have shown preliminary promising results. In adults IL-6 and IL-10 seem to have a favorable potential to become a good biomarker to identify OSA.

Introduction

Obstructive sleep apnea (OSA) has now been widely recognized as a major public health concern with numerous and widespread societal consequences that include among others, motor vehicle accidents, increased cardiovascular morbidity, heightened risk for metabolic dysfunction, and mood, behavioral and cognitive deficits leading to impaired work performance and productivity [1]. Although healthcare costs are not normally distributed, i.e., the costliest and the sickest tertile of patients consume 65–82% of all medical-related costs, it has now become apparent that OSA significantly adds to the healthcare cost burden, in addition to its adverse impact on the economy [2,3]. It is notable that sleep disorders have been assigned as playing a causative role in an estimated 9.1% of work-related injuries [4].

The prevalence of OSA varies widely, ranging from 14.7% to 36.5%, depending on gender and nationality [5]. It is higher in males (34.2%) than in females (14.7%) [5]. Although the prevalence of OSA in Hispanics (36.5%) is similar to American Whites (33.3%), increased risk of OSA occurs in both African American and Asian ethnic groups [5–8]. In contrast, the prevalence of pediatric OSA is

* Corresponding author. Department of Pediatrics, The University of Chicago, 5721 S. Maryland Avenue, MC 8000, Suite K-160, Chicago, IL 60637, USA. Tel.: +1 (773) 702 3360; fax: +1 (773) 926 0756.
E-mail address: dgozal@uchicago.edu (D. Gozal).

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Abbreviation

AAP	American Academy of Pediatrics
AHI	apnea/hypopnea index
AI	apnea index
CRP	C-reactive protein
EBC	exhaled breath condensate
EPISONO	Epidemiologic sleep study
hr/TST	hour total sleep time
hs-CRP	high sensitivity C-reactive protein
IL-6	interleukin-6
OAHI	obstructive apnea–hypopnea index
OAI	obstructive apnea index
OSA	obstructive sleep apnea
OR	odds ratio
PSG	polysomnography
RR	risk ratio
sIL-6R	soluble interleukin-6 receptor
TNF-α	tumor necrosis factor α

reported to be between 1 and 4%, with the caveat that prospective community-based studies using overnight polysomnography (PSG) are lacking [9,10].

The standard diagnostic procedure for establishing the presence of OSA is the overnight polysomnography [11]. Except for the *a priori* reported consensus [11], an original publication or study that provided definitive validation on the use of overnight PSG as the gold standard in OSA diagnosis could not be found even after an extensive literature search. However, notwithstanding the great progress in our understanding of sleep disorders that PSG have afforded over the years, it has also become apparent that overnight PSG are onerous and labor-intensive tests that impose substantial inconvenience to the patients, and are relatively inaccessible. Indeed, waiting times between referral for evaluation to diagnosis commonly take 3–6 mo across the United States and around the world [12].

The relative complexity and high costs associated with overnight PSG as the gold standard approach employed for diagnosing the vast majority of sleep disorders has spurred the quest for alternative diagnostic methods [12]. The development of simple, cheap, and reliable screening tools that permit precise screening of at-risk populations is paramount. If accurate identification of those subjects with or without definitive disease is accomplished using such simplified and less onerous tools, then timely access to clinical care would be possible to a large sector of the population [12].

During the search for this elusive screening tool, special interest has centered around potential OSA biomarkers. The ideal biomarker should be highly sensitive and specific for OSA, should be dose-responsive and correlate to severity of disease, and should be involved in an important causal pathway, so that changes in the biomarker levels reliably predict improvements in the outcome [13]. Several different OSA biomarkers have been proposed over the last 14 y. However, to the best of our knowledge, no scoping review has been conducted thus far to critically examine what we currently know on the potential viability and use of biomarkers in OSA diagnosis and management. Therefore, the purpose of this study was to map our current understanding regarding biomarkers, and provide assessments of their characteristics in the context of OSA in both adults and children, to identify gaps in the research and help with the dissemination of the findings, and to determine the value of conducting a full systematic review related to this topic.

Methods

This scoping review was done adhering to Arksey and O'Malley's scoping review proposed reporting framework [14].

Research question

A scoping review of studies in humans without age restriction that evaluated the potential diagnostic value of biological markers (blood, exhaled breath condensate (EBC), salivary, and urinary) in the diagnostic process of OSA syndrome was undertaken.

Identification of relevant studies

Inclusion criteria

Retained articles were only those studies whose objective was to identify associated biomarkers in subjects with OSA, the latter being confirmed with a full overnight PSG or home-based PSG. Only studies that performed PSG in all subjects were included. The selected studies could include studies in obese and cardiac patients. Studies that assessed the impact of treatment were also included. Studies with and without a control group were selected. Only studies in English, Spanish and Portuguese language were considered.

Exclusion criteria

Studies using day PSG or multichannel polygraphy as the reference diagnostic standard were not included. Studies using biomarkers only to detect the presence of OSA-associated morbidities (cognitive, excessive sleepiness, cardiovascular, metabolic) and/or in which the sample included genetic syndromic patients (e.g., Down syndrome, craniofacial anomalies, neuromuscular disorders, etc.), or a cohort of patients with a primary disease for which OSA prevalence is being investigated (e.g., patients with kidney disease, and/or rheumatologic conditions) were omitted. Reviews, letters, conference abstracts and personal opinions were not considered.

Detailed individual search strategies for each of the following bibliographic databases were developed: Cochrane, Embase, MEDLINE, PubMed, and LILACS. A partial grey literature search was undertaken using Google Scholar. The end search date for all database searches was March 20, 2014. The references cited in the selected articles were also checked for any citation that could have been missed during the electronic database searches. Additional studies were obtained from a well-published expert in sleep medicine.

Appropriate truncation and word combinations were selected and were adapted for each database search (Appendix 1). All references were managed by reference manager software (RefWorks-COS is a business unit of ProQuest, LLC. ©7200 Wisconsin Avenue, Suite 601 Bethesda, MD 20866 USA) and duplicate hits were removed.

Study selection

The selection was completed in two phases. In phase 1, two reviewers independently reviewed the titles and abstracts of all identified electronic database citations (GDL and CPP). A third author was involved when required to make a final decision (SA). Any studies that appeared not to fulfill the inclusion criteria were discarded. In phase 2, the same selection criteria were applied to the full articles to confirm their eligibility. The same two reviewers (GDL and CPP) independently participated in phase 2. The reference list of all included articles was reviewed by one examiner (GDL). The articles selected were read by both examiners (GDL and CPP).

Any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers (GDL, CPP, SA). A fourth author with extensive professional experience in sleep medicine (DG) was involved when controversy arose before making a final decision. Final selection was always based on the full-text of the publication.

Charting the data

For all included studies the following information was recorded: year of publication, author, country, sample size, age, name and type of biomarkers, diagnostic PSG-based measure, results, and main conclusion. Authors of potentially eligible full-articles were contacted as necessary to provide further details about their studies.

One author (GDL) collected the required information from the selected articles. A second author (CPP) cross-checked all the collected information. Again, any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers (GDL, CPP, SA). A fourth author (DG) was involved, when required, to make a final decision.

Level of evidence

The methodology of selected studies was classified using a non-validated adaptation of the evidence quality criteria from American Academy of Pediatrics (AAP) [11]. Two reviewers (GDL and CPP) independently classified the studies into A (well-designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly

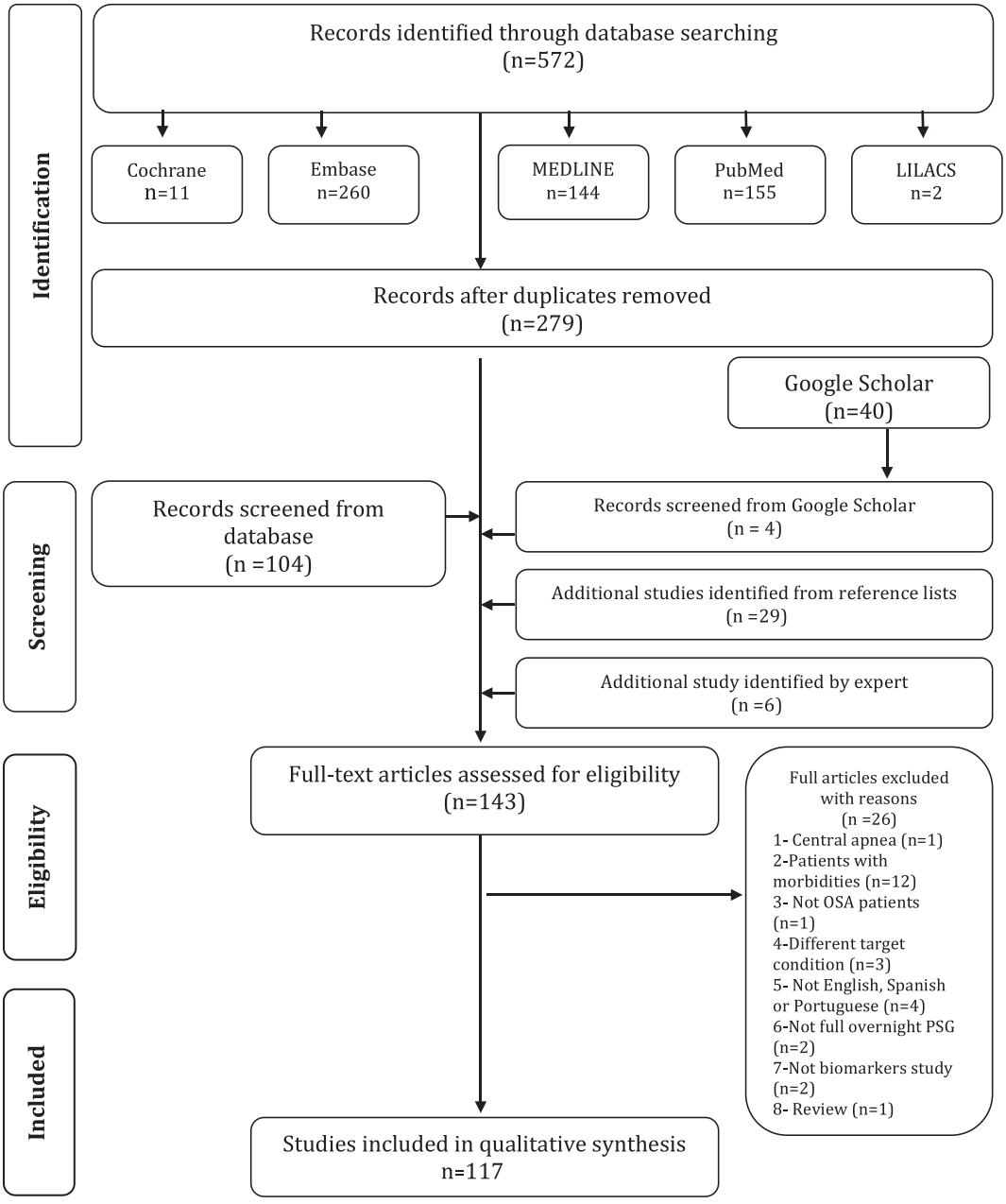

Fig. 1. Flow diagram of literature search and selection criteria.

consistent evidence from observational studies), and C (observational studies (case-control and cohort design). Disagreements were resolved by a third reviewer (DG).

Additionally the biomarker clinical application was classified as 1) potential diagnostic biomarker(s) 2) when the evidence was inconclusive for diagnostic biomarker, and 3) if the evidence was not supportive as potential diagnostic biomarker(s). Two reviewers (GDL and CPP) independently classified the clinical application of biomarkers. A third reviewer (SA) reviewed the classification. Disagreements were resolved by a fourth reviewer (DG).

Collating, summarizing and report the results

Any outcome measurement was considered: risk ratio (RR), odds ratio (OR) or risk difference for dichotomous outcomes; mean difference or standardized mean difference for continuous outcomes; sensitivity and specificity in diagnostic studies.

Results

Study selection

In phase 1, we found 572 citations across the five electronic databases. After duplicate articles were removed, 279 remaining different citations were retained. A comprehensive evaluation of the abstracts was performed and resulted in a final number of 104 articles after phase 1. We found 40 citations in Google Scholar, but only four articles from Google Scholar met our phase 1 inclusion criteria. We identified 29 additional studies from the hand-search of reference lists of these studies, and added six more articles received by an expert (DG). Therefore, we retrieved 143 articles to conduct a full-text review, and subsequently excluded 26 studies [15–40] (Appendix 2). Thus, a total of 117 articles were selected. A flow chart of the process of identification, inclusion, and exclusion of studies is shown in Fig. 1.

Study characteristics

The selected studies were grouped into two categories: studies involving children (≤18 years of age) and adults (>18 years of age). Eighty-two studies were conducted in adults and 34 studies involved children (with the exception of one study that included individuals between 12 and 22 years old [41]). One study had a sample composed of both adults and children [42].

The pediatric studies were published between 2002 and 2014. They were conducted in the USA [41–60], Greece [61–65], China [66–68], South Korea [69–71], Italy [72,73], Brazil [74], and Hungary [75]. (Fig. 2) The diagnostic criterion for OSA was established based on the apnea index (AI), apnea/hypopnea index (AHI), obstructive apnea index (OAI), obstructive apnea–hypopnea index (OAHI), and respiratory disturbance index (RDI). Occasionally, the specific PSG measure used to reach the diagnosis of OSA was not reported [61,64]. When the authors used AHI, the AHI ranged from AHI >1 to AHI >5/hrTST. Most of the studies assessed blood biomarkers [41–44,46,49–52,54–57,59–62,66–68,74], while seven studied urinary biomarkers [47,48,53,58,63,64,73], four explored for potential biomarkers in saliva [69–72], and three studies involved EBC [45,65,75]. A summary of the study descriptive characteristics can be found in Table 1. Complementary information regarding these studies is reported in Appendix 3.

The studies in adults were published between 2000 and 2014. The majority was published in China [76–87], USA [42,88–98], and Japan [99–109] (Fig. 3). The OSA diagnostic criterion was established by AHI, and RDI and occasionally [89,92,93,99,100,104,110–112] it was not specifically reported. When the authors used AHI, the AHI ranged from AHI >5 to AHI ≥30/hrTST. Most of the studies assessed blood-based biomarkers [42,76,79–102,105–111,113–148], two focused on urinary biomarkers [103,104], and two explored for biomarkers in EBC [149,150], while only one study examined saliva [112]. Five studies used both blood and urine [77,151–154] and four studies used blood and EBC [78,155–157]. A summary of the study descriptive characteristics can be found in Table 2. Complementary information regarding these studies is reported in Appendix 4.

Level of evidence

In studies involving children, nearly all studies were classified as B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies). Only one study [44] was classified as C (case-control and cohort design).

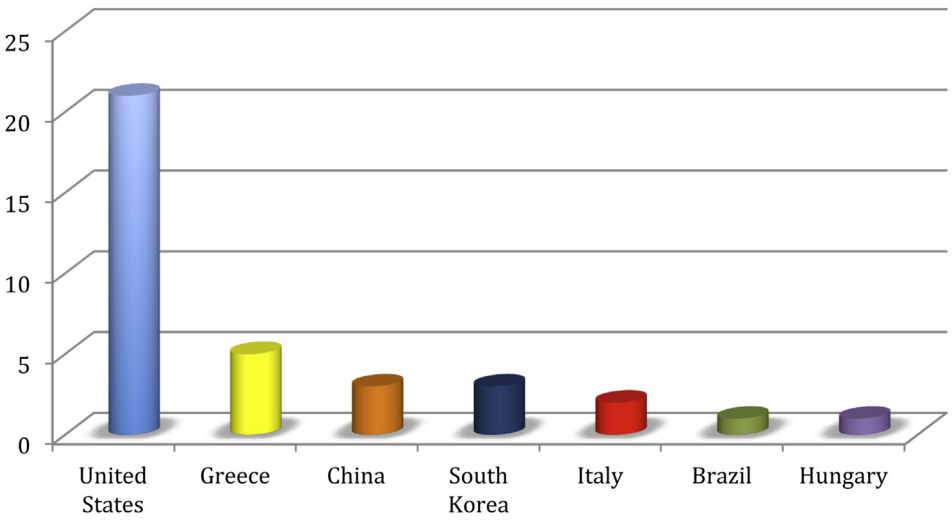

Fig. 2. Distribution of children studies according to country ($n = 35$). United States ($n = 21$), Greece ($n = 5$), China ($n = 3$), South Korea ($n = 3$), Italy ($n = 2$), Brazil ($n = 1$), Hungary ($n = 1$).

Table 1
Summary of study descriptive characteristics of included pediatric articles ($n = 35$). The biomarker clinical application was classified as 1) potential diagnostic biomarker(s) 2) inconclusive for diagnostic biomarker, and 3) evidence not supportive as potential diagnostic biomarker(s). The level of evidence was classified in A (well designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies (case-control and cohort design)).

Year	Author	Country	Cases	Control	Mean age or range if provided	Type of biomarker	OSA diagnostic criteria (PSG)	Biomarker	Classification as a biomarker	Level of evidence
2002	Gozal et al. [42]	United States	OSA ($n = 41$/23 male)	–	7.6	Blood	AI > 5	VEGF	2	B
2004	Tauman et al. [43]	United States	Consecutive snoring OSA ($n = 66$/37 male)	Consecutive snoring non-OSA ($n = 15$/10 male)	3–18 (9.3)	Blood	AHI ≥ 5	CRP	2	B
2005	Kaditis et al. [61]	Greece	AHI ≥ 5 ($n = 30$/17 male)	AHI < 5 ($n = 80$/47 male)	2–13	Blood	Not reported	HOMA	3	B
2005	Larkin et al. [44]	United States	Mild OSA ($n = 143$) Moderate OSA (AHI 5–15) Severe OSA (AHI ≥15)	–	13–18	Blood	AHI > 1	CRP	2	C
2006	Goldbart et al. [45]	United States	Snoring ($n = 50$): Mild OSA ($n = 29$/58% male) OSA ($n = 21$/57% male)	Non-snoring ($n = 12$/58% male)	6–16	EBC	AHI > 5	PGE_2, LTB_4, Cys-LTs, LTC_4, LTD_4, LTE_4	2 (LTB_4, Cys-LTs, LTC_4, LTD_4, LTE_4) 3 (PGE_2)	B
2006	Kheirandish-Gozal et al. [46]	United States	Non-obese with OSA before and after adenotonsillectomy ($n = 20$/55% boys)	–	7.3	Blood	AHI ≥ 5	CRP	2	B
2006	Krishna et al. [47]	United States	Snoring or suspected OSA ($n = 11$/9 male)	Healthy non-snoring ($n = 11$/8 male)	3–14 (6.8)	Urine	AHI > 5	Proteomic analysis	2	B
2006	Li et al. [66]	China	Obese with Mild OSA: AHI: 1–10 ($n = 47$) Moderate to Severe OSA: AHI >10 ($n = 13$)	Non-OSA snoring: AHI < 1 ($n = 34$)	7–18	Blood	AHI > 1	Lipid profile, insulin	1 (insulin)	B
2006	Montgomery-Downs et al. [48]	United States	OSA ($n = 47$)	–	6.6	Urine	OAHI ≥ 1	IsoP-m	3	B
2006	O'Brien et al. [49]	United States	Mild OSA ($n = 47$/64% male) OSA ($n = 39$/44% male)	Non-OSA ($n = 42$/43% male)	4–10 (6.9)	Blood	AHI > 5	ICAM-1, P-selectin	1 (P-selectin) 3 (ICAM-1)	B
2006	Shah et al. [50]	United States	OSA ($n = 20$)	Non-OSA with HS ($n = 20$)	3–12	Blood	AHI > 5	Proteomic patterns	1	B
2007	Kaditis et al. [62]	Greece	PS ($n = 19$) Mild OSA ($n = 30$) OSA ($n = 25$)	–	3–13	Blood	AHI > 1	cICAM-1	3	B
2007	Tauman et al. [51]	United States	Mild OSA ($n = 42$) OSA ($n = 43$)	Non-OSA ($n = 45$)	1–17 (8.2)	Blood	AHI > 1	Leptin, adiponectin, glucose, insulin, CRP	3	B
2008	Gozal et al. [52]	United States	Non-obese OSA ($n = 20$/12 male)	Non-snoring ($n = 20$/12 male)	4–9	Blood	AHI > 1	IL-6 IL-10	2	B
2008	Li et al. [68]	China	Mild OSA ($n = 23$) Moderate OSA ($n = 22$)	Non-OSA ($n = 96$)	8.5–12.8	Blood	OAI > 1	CRP	2	B
2009	Gozal et al. [53]	United States	PS ($n = 30$/16 male) OSA ($n = 60$/32 male)	Non-OSA ($n = 30$/16 male)	2–9	Urine	OAI > and/or OAHI > 2	Kallikrein-1, uromodulin, urocortin-3, orosomucoid-1	1	B
2009	Kaditis et al. [63]	Greece	PS ($n = 26$) Mild OSA ($n = 29$) Moderate to severe OSA ($n = 19$)	History of recurrent tonsillitis and without snoring ($n = 18$)	6.0	Urine	OAHI ≥2	Cys-LTs	2	B
2009	Kaditis et al. [64]	Greece	Mild hypoxemia ($n = 22$/9 male) Moderate hypoxemia ($n = 20$/11 male) Severe hypoxemia ($n = 12$/9 male)	Non-snoring ($n = 10$/7 male)	5.2	Urine	Not reported	Norepinephrine, Epinephrine, Normetanephrine, Metanephrine	2	B

2010	Kim et al. [54]	United States	Mild OSA (n = 106/60.4% male) Moderate-to-severe OSA (n = 34/61.8% male)	Non- OSA (n = 115/55.7% male)	5–10 (7.6)	Blood	AHI ≥ 1	MRP 8/14	2	B
2010	Li et al. [67]	China	HS and OSA symptoms (n = 141/96 male).	–	8.5–12.8	Blood	OAI > 1	Adipokines	3	B
2011	Bhushan et al. [55]	United States	OSA Non-Obese (n = 92) OSA Obese (n = 94)	Non-OSA Non- Obese (n = 90) Obese (n = 33)	5–8	Blood	AHI ≥ 1	FABP4	2	B
2012	DeBoer [41]	United States	OSA (n = 9/4 male)	Non-OSA (n = 15/10 male)	12–22	Blood	AHI > 2.5	hsCRP	3	B
2012	Khalyfa et al. [56]	United States	OSA (n = 131)	Non-OSA (n = 323)	5–8	Blood	OAI ≥ 1 and AHI ≥ 5	MIF, hsCRP, insulin, glucose	1	B
2012	Malakasioti et al. [65]	Greece	Mild OSA (n = 22/11 male) Moderate-to severe OSA (n = 12/6 male)	Non-OSA (n = 16/8 male)	4–14	EBC	AHI > 1	H_2O_2 Sum of nitrate NO_x	2	B
2012	Stefanini et al. [74]	Brazil	OSA (n = 28)	Non-OSA with HS (n = 22)	3–13	Blood	AHI ≥ 1	Hemoglobin, hematocrit, glucose, insulin, triglycerides, total cholesterol, HDL, LDL, VLDL, TSH, T4	3	B
2013	Benedek et al. [75]	Hungary	OSA (n = 18)	Non-OSA with HS (n = 10)	8.5	EBC	AHI ≥ 1	VOCs mixtures	1	B
2013	Gozal et al. [57]	United States	OSA with endothelial dysfunction (n = 35) OSA without endothelial dysfunction (n = 47)	Healthy Non-OSA (n = 35)	5–10 (7.2)	Blood	AHI ≥ 2	Plasma adropin	3	B
2013	Kheirandish-Gozal et al. [58]	United States	OSA (n = 50)	Non-OSA (n = 20)	3–12 (6.3)	Urine	AHI ≥ 2	Urinary neurotransmitters	1	B
2013	Kim et al. [59]	United States	Mild OSA (n = 53) Moderate to severe OSA (n = 9)	Non- OSA (n = 44)	5–10	Blood	AHI ≥ 1	TREM-1, pentraxin-3, hsCRP, MRP 8/14	2	B
2013	Park et al. [69]	Korea	OSA (n = 48/32 male)	Non-OSA, (n = 32/13 male)	3–13 (7.1)	Saliva	AHI > 1	Salivary cortisol (r-sCor, n-sCor, m-sCor)	2 (m-sCor, r-sCor) 3 (n-sCor)	B
2014	Jeong et al. [70]	Korea	OSA with enlarged tonsils/adenoids (n = 13/11 male)	–	3–11	Saliva	AHI > 1	Salivary cortisol (n-sCor, m-sCor, sub-sCor, r-sCor)	1	B
2014	Kheirandish-Gozal [60]	United States	OSA Non-obese (n = 57/54.3% male) OSA obese (n = 53/58.5% male)	Non-OSA non-obese (n = 59/54.2% male) Non-OSA/obese (n = 50/54% male)	6.8	Blood	AHI ≥ 2	LBP	1	B
2014	Park et al. [71]	Korea	OSA with enlarged tonsils/adenoids (n = 41/30 male)	OSA with enlarged tonsils/adenoids (n = 26/9 male)	3–16	Saliva	AHI ≥ 1	Alpha-amylase	1	B
2014	Patacchioli et al. [72]	Italy	Mild OSA (n = 13) Moderate-to-severe OSA (n = 14)	Non-OSA (n = 7)	4.9	Saliva	AHI > 1	Salivary cortisol a-amylase diurnal trajectory and production	2 (salivary cortisol) 3 (a-amylase diurnal trajectory and production)	B
2014	Villa et al. [73]	Italy	AHI < 5 (n = 28/21 male) AHI ≥5 (n = 37/20 male)	–	5.9	Urine	AHI ≥ 5	8-isoprostane	1	B

No study was classified as A (well designed prognostic or diagnostic studies on relevant population).

In adult-based studies, 70 were classified as B, with 11 studies being classified as C. Only three studies were classified as fulfilling A criteria [91,131,143].

Synthesis of results

When biomarkers were classified according to their clinical application, the biomarkers studied in nine pediatric studies were designated as potential diagnostic biomarkers; in 15 studies, findings were inconclusive for a diagnostic biomarker, and eight studies presented evidence that was not supportive as potential diagnostic biomarkers. Three studies had different classifications for two biomarkers studied. The classification for each study is presented in Table 1. All potential biomarkers for pediatric OSA are presented in Table 3.

In studies involving adults, classification of the biomarkers according to their clinical application yielded 58 studies where the biomarkers were considered as potential diagnostic biomarkers, while 19 studies were inconclusive for diagnostic biomarkers, and three studies presented evidence not supportive as potential diagnostic biomarkers. One study had different classifications for two biomarkers concomitantly studied. Regarding the potential diagnostic biomarkers, interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and high sensitivity C-reactive protein (hsCRP) were the most frequently assessed biomarkers. The classification for each study is presented in Table 1. The potential biomarkers for adults identified are shown in Table 4.

Discussion

The present scoping review investigated the available evidence regarding biomarkers for the diagnosis of OSA. The gold standard for OSA-PSG-imposes several important limitations, such as cost and reduced widespread availability. Moreover, this technique is potentially inconvenient since it requires that the patient will sleep outside the home environment [158]. Therefore, we need to develop methods that would allow for the large-scale screening of at-risk populations, and enable the accurate identification of the subjects with or without the disease, could potentially revolutionize the field [12]. This pressing need to find an ideal biomarker for OSA as an alternative to the PSG may account for the large number of studies that have addressed this topic since 2000. In addition, the realization that OSA is associated with elevated levels of biochemical or inflammatory markers that may contribute to an increased risk of cardiovascular disease further propelled the field forward in the quest for diagnostic biomarkers [128].

The ideal biomarker should have some critical characteristics, such as disease specificity, mandatory presence in all affected patients (i.e., high sensitivity and specificity), reversibility following proper treatment, and detectability before patients develop obvious clinical manifestations. Furthermore, ideal biomarkers should reflect not only the severity of the disease, but also provide indicative information over the cumulative history of the disease, as well as enable a cut-off value with minimal overlap between normal and disease [159]. In addition, an optimal diagnostic policy employing biomarkers would be expected to minimize the total cost and burden of diagnosing a patient, in which the economic value would consist of the sum of two financially-driven components, namely measurement costs and the costs associated with misdiagnosis [160].

Before we discuss the actual findings of this scoping review, some technical and methodological considerations regarding the

*All terms that mean obstructive sleep apnea (SDB, SRDB, OSAS) were standardized as OSA.
Abbreviations: AHI = apnea/hypopnea index, cICAM-1 = circulating intercellular adhesion molecule 1, CRP=C reactive protein, Cys-LTs = cysteinyl leukotrienes, EBC = exhaled breath condensate, FABP4 = fatty acid binding protein 4, H_2O_2 = hydrogen peroxide, HDL = high density lipoprotein, HOMA = homeostasis model assessment, HS = habitual snoring, hsCRP = high-sensitivity C-reactive protein, ICAM-1 intercellular adhesion molecule 1, IL-10 = interleukin-10, IsoP-m = isoprostane metabolites, LBP = lipopolysaccharide-binding protein, LTB_4 = leukotriene B_4, LTC_4 = leukotriene C_4, LTD_4 = leukotriene D_4, LTE_4 = leukotriene E_4, m-sCor = salivary cortisol after, PSG morning salivary cortisol, MIF = macrophage migration inhibitory factor, MRP = myeloid-related protein, n-sCor = salivary cortisol before PSG night salivary cortisol, NO_x = nitrate mono-nitrogen oxides, OAHI = obstructive apnea-hypopnea index, OAI = obstructive apnea index, OSA = obstructive sleep apnea, Ptx3 = pentraxin-3, PGE_2 = prostaglandin E_2, PS = primary snoring, PSG = polysomnography, r-sCor = salivary cortisol ratio, subsCor = subtract salivary cortisol, T4 = thyroxine, TREM-1 = triggering receptor expressed on myeloid cells-1, TSH = thyroid stimulating hormone, VEGF = vascular endothelial growth factor, VLDL = very low density lipoprotein, VOCs = complex volatile organic compounds.

studies included merit specific commentary. Different groups of researchers have attempted to identify OSA biomarkers in children and adults throughout the world. Interestingly, most of the pediatric studies have been performed in United States and Greece, primarily by two major research groups led by Gozal and Kaditis, respectively, while most studies involving adults have been conducted in China, the United States and Japan, with no particular predominance of any specific group of investigators. Studies in adults have primarily focused on the investigation of IL-6, TNF-α, and hsCRP. On the other hand, we did not find any particular trend towards a specific biomarker among the pediatric studies. Also noteworthy was the wide variation in the OSA diagnostic criteria employed by the pediatric studies. The AHI was the most frequently used diagnostic PSG measure of OSA severity. However, the use of AHI was associated with two major limitations. Firstly, the clinically accepted consensus for the cut-off AHI value for either the presence or absence of OSA remains unresolved. Secondly, no widely accepted agreement has been reached regarding whether children with PSG-based AHI values between the "normal cutoff" and 5/hrTST should undergo surgical adenotonsillectomy [159]. Based on these considerations, it becomes apparent that the definitive diagnosis of OSA solely based on the low-end spectrum of the PSG-based measures (i.e., AHI, RDI, OAHI, etc.) is difficult if not impossible. It is also apparent that the lack of consensus on the PSG-based diagnostic criteria is the result of the relative dichotomy that exists between PSG-derived measures and clinical symptoms. For example, children who are very symptomatic may present with a "normal PSG" in the presence of habitual snoring. Conversely, asymptomatic snoring children may exhibit severe respiratory disturbance in their PSG [160]. Similar, albeit less vague overlap exists among adult patients, even if the PSG criteria for the presence of OSA have been more firmly established and accepted around the world [161–166].

Regarding the type of biomarkers explored in our assessment, the majority of studies evaluated blood biomarkers, with only few studies having evaluated either urine, saliva and/or EBC, although such approaches are noninvasive and easily collected, and particularly suitable for children. Analyzing the level of evidence, only three studies were classified as A [91,131,143]. Mehra et al. [91] evaluated biomarkers in participants of the Cleveland Family Study, a longitudinal genetic epidemiological study in United States. This study was designed to investigate the causal factors and natural history of OSA. Svensson et al. [131] selected women from general population in Sweden. Hirotsu et al. [143] used subjects from an epidemiologic sleep study namely EPISONO, in Brazil. Considering these three studies [91,131,143], we are able to identify only two potential biomarkers: sIL-6R [91] and uric acid [143]. Most studies were classified as level of evidence B, because they used samples from sleep laboratories or patients with suspected OSA rather than community-based approaches.

In the context of the properties of potential diagnostic biomarkers, the importance of reporting receiver operator curves and other measures of diagnostic performance can not be overemphasized [158]. However, even though it is impossible to properly assess the real diagnostic capability of any alternative test without such measures, we found only nine studies that reported sensitivity and specificity. The sensitivity and specificity for these nine studies [50,53,58,75] [78,82,117,120,143] varied substantially from 43% to 100%, and from 45% to 100%, respectively. Only five studies reported excellent sensitivity: Li et al. [78](100%), Gozal et al. [53] (95%), Shah et al. [50] (93%), Guo et al. [82] (91%) and Kheirandish-Gozal et al. [58] (82%). From these five studies [50,53,58,75,82], only Gozal et al. [53] and Li et al. [78] also reported excellent specificity (both 97%). It is important to emphasize that the results reported when the biomarkers were combined in Gozal et al. [53] and Kheirandish-Gozal et al. [58] showed better accuracy measurements than when the biomarkers tested in these studies were analyzed individually.

In summary, this review provides up-to-date insights of the current state of knowledge about biological markers and their potential applicability in OSA diagnosis. Over the last 14 years, a substantial number of studies have aimed to identify an ideal biomarker or set of biomarkers for OSA. Although, no simple and useful disease marker panel for OSA is currently available and routinely used in clinical practice, considerable progress has been

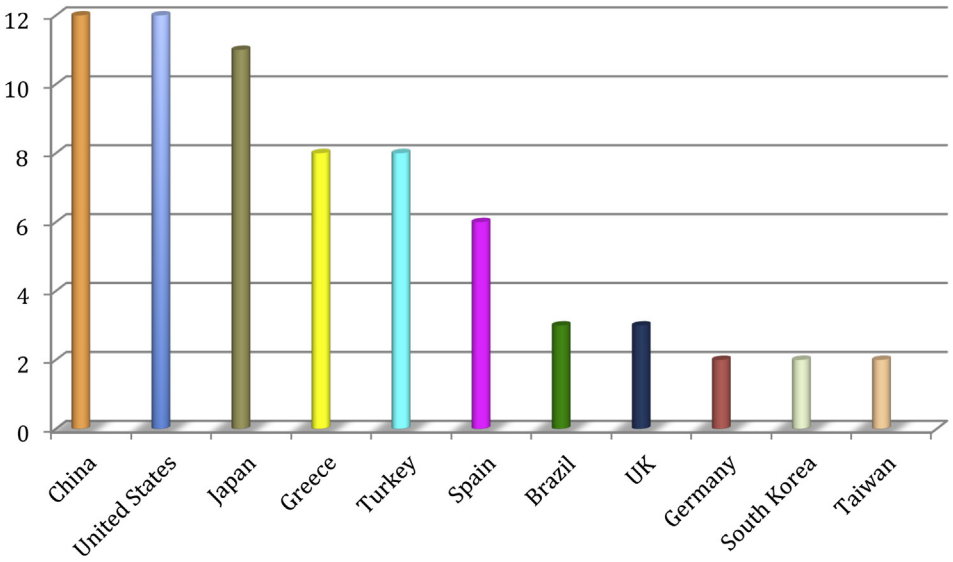

Fig. 3. Distribution of adults' studies according to country ($n = 83$). China ($n = 12$), United States ($n = 12$), Japan ($n = 11$), Greece ($n = 8$), Turkey ($n = 8$), Spain ($n = 6$), Brazil ($n = 3$), UK ($n = 3$), Germany ($n = 2$), South Korea ($n = 2$), Taiwan ($n = 2$). In the following countries only one study was done: Arabia, Australia, Canada, France, India, Ireland, Israel, Israel/Sweden, Italy, Poland, Portugal, Sweden, Switzerland, Thailand. These countries are not represented in the graph.

Table 2
Summary of study descriptive characteristics of included articles (adults, $n = 83$) The biomarker clinical application was classified as [1] potential diagnostic biomarker(s) [2]; inconclusive for diagnostic biomarker, and [3] evidence not supportive as potential diagnostic biomarker(s). The level of evidence was classified in A (well designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies (case-control and cohort design)).

Year	Author	Country	Cases[a]	Controls	Age (mean in years)	Type of biomarker	OSA diagnostic criteria at PSG	Biomarker	Classification as a biomarker	Level of evidence
2000	Chin et al. [99]	Japan	OSA patients treated with CPAP ($n = 23$/23 male)	–	51.0	Blood	Not reported	Soluble intercellular adhesion molecules	2	B
2002	Carpagnano et al. [149]	UK	OSA ($n = 18$/13 male) Obese ($n = 10$/4 male)	Healthy adults ($n = 15$/8 men)	41.7[b]	EBC	AHI >20	IL-6, 8-isoprostane	1	B
2002	Gozal et al. [42]	United States	OSA ($n = 68$/47 male)	–	54.4	Blood	AHI ≥15	VEGF	1	B
2002	Lavie et al. Study 1 [110]	Israel and Sweden	OSA ($n = 85$)	–	52.8	Blood	Not reported	VEGF	2	B
2002	Lavie et al. Study 2 [110]	Israel and Sweden	Severe OSA ($n = 5$)	Control group 1: healthy adults ($n = 6$) Control group 2: snoring OSA suspected but AHI <10 ($n = 6$)	40.0[b]	Blood	AHI ≥10	VEGF	2	B
2002	Lavie et al. Study 3 [110]	Israel and Sweden	CPAP patients ($n = 22$)	–	54.3	Blood	Not reported	VEGF	2	B
2002	Schulz et al. [114]	Germany	OSA with severe hypoxia ($n = 10$) OSA with moderate hypoxia ($n = 10$)	Non-OSA ($n = 10$)	Not reported	Blood	AHI >10	VEGF	1	B
2002	Shamsuzzaman et al. [88]	United states	OSA ($n = 22$/18 male)	Non-OSA ($n = 20$/15 male)	45.5[b]	Blood	AHI ≥5	CRP	1	B
2003	Carpagnano et al. [155]	UK	OSA ($n = 18$/13 male)	Non-OSA ($n = 12$/8 male)	47.0[b]	Blood EBC	AHI >20	8-Isoprotane	1	B
2003	Christou et al. [113]	Greece	OSA ($n = 17$/16 male)	Non-OSA ($n = 8$/4 male)	51.4[b]	Blood	AHI >10	Antioxidant capacity	2	B
2003	Ohga et al. [100]	Japan	OSA ($n = 20$/20 male)	Non-OSA ($n = 10$/10 male)	48.35[b]	Blood	Not reported	ICAM-1, IL-8, MCP-1	1	C
2003	Yokoe et al. [101]	Japan	Mild OSA ($n = 13$) Moderate to severe OSA ($N = 17$)	Obese subjects ($n = 14$/14 male)	51.2[b]	Blood	AHI >5	CRP, IL-6	1	B
2004	Guilleminault et al. [89]	United states	OSA ($n = 146$) and UARS ($n = 39$)	Control ($n = 54$)	43.8[b]	Blood	Not reported	CRP	2	B
2004	Imagawa et al. [102]	Japan	Severe OSA ($n = 110$)	Non-OSA ($n = 45$)	Not reported	Blood	AHI ≥30	IL-6, TNF-α	2	C
2005	Alzoghaibi et al. [115]	Saudi Arabia	Nonsmoker patients with severe OSA ($n = 25$)	Healthy nonsmokers ($n = 17$)	40.1[b]	Blood	AHI ≥ 5	SOD, Lipid peroxidation, Cytokines, IL-8, GCP-2	3 (SOD Lipid peroxidation Cytokines) 1 (IL-8 GCP-2)	B
2005	Sukegawa et al. [103]	Japan	OSA ($n = 17$/17 male)	–	53.7	Urine	AHI ≥5	Urinary catecholamines	2	B
2005	Yamauchi et al. [104]	Japan	Non-severe OSA ($n = 70$) Severe OSA ($n = 58$)	–	49.1[b]	Urine	Not reported	8-OHdG	1	B
2006	Braga et al. [116]	Brazil	OSA ($n = 29$/29male)	Non-OSA ($n = 17$/17 male)	36.5[b]	Blood	AHI ≥ 5	S100B, NSE	1	B
2006	Htoo et al. [90]	United states	Mild to moderate OSA ($n = 6$/4 male) Severe OSA ($n = 7$/6 male)	Non-OSA ($n = 9$/6 male)	39.2[b]	Blood	AHI >10	NF-kB	1	B

2006	Lentini et al. [117]	Germany	Mild to moderate OSA ($n = 93/17$ male) Severe OSA ($n = 89/71$ male)	Non-OSA ($n = 19/8$ male)	54.9	Blood	AHI >5	CK levels	1	B
2006	Mehra et al. [91]	United States	RDI 0–4.9 ($n = 177/58$ male) RDI 5.0–9.9 ($n = 50/22$ male) RDI 10-14.9 ($n = 39/17$ male) RDI 15.0-29.9 ($n = 62/29$ male)	–	46.9[b]	Blood	RDI ≥5	IL-6, slL-R	1 (slL-R) 3(IL-6)	A
2007	Peled et al. [118]	Israel	OSA ($n = 100/61$ male)	–	58.1	Blood	AHI ≥10	VEGF	3	B
2007	Phillips et al. [151]	Australia	Subjects after one and seven nights of withdrawal from CPAP ($n = 20/19$ male)	–	54.0	Blood Urine	RDI ≥15	hsCRP, hsIL-6 and hsTNF-α, VEGF, urinary catecholamines	1 Noradrenaline 3(hsCRP, hsIL-6 and hsTNF-α, VEGF, Adrenaline	B
2007	Punjabi et al. [92]	United States	OSA ($n = 69/69$ male)	–	40.2	Blood	Not reported	CRP	2	B
2007	Ryan et al. [119]	Ireland	Mild/Moderate OSA ($n = 35$) Severe OSA ($n = 31$) Severe Obese OSA ($n = 14$)	Non-OSA ($n = 30$)	41.3[b]	Blood	AHI >5	CRP, Homocysteine	3	C
2007	Ursavas et al. [120]	Turkey	Moderate-to-severe OSA ($n = 39/30$ male)	Non-OSA ($n = 34/23$ male)	50.5[b]	Blood	AHI ≥5	ICAM-1, VCAM-1	1	B
2007	Ye et al. [76]	China	Mild OSA ($n = 23/23$ male) Moderate to severe OSA ($n = 28/28$ male)	Obese men ($n = 25$)	49.8[b]	Blood	AHI ≥ 5	CRP, MMP-9	1	B
2008	Antonopoulou et al. [156]	Greece	OSA ($n = 45/37$ male, 28 smokers)	Healthy subjects non-ramdomly selected ($n = 25/18$ male, 15 smokers)	51.5[b]	Blood EBC	AHI ≥ 5	EBD: pH, 8-isoprostane, TNF-α, IL-6 Plasma: leptin	3	B
2008	Arias et al. [152]	Spain	OSA ($n = 30/30$ male)	Obese subjects ($n = 15/15$ male)	50.0[b]	Blood Urine	AHI ≥10	sTNFR-1, IL-6, LTB4, TNF-α, Norepinephrine, Epinephrine	1 sTNF, Norepinephrine Epinephrine) 3(R-1 IL-6 LTB4 TNF-α)	B
2008	Burioka et al. [105]	Japan	Severe OSA ($n = 9/9$ male)	–	48.2	Blood	AHI >5	IL-6	1	B
2008	Constantinidis et al. [121]	Greece	Obese OSA ($n = 13/13$ male) Overweight OSA ($n = 11/11$ male)	Overweighted ($n = 12/12$ male) and obese ($n = 15/15$ male)	26-54 (45.1)	Blood	AHI >5	IL-1β, IL-6, TNF-a	1(IL-6 TNF-a) 3 (IL-1β,)	B
2008	Kanbay et al. [122]	Turkey	OSA ($n = 106$)	Non-OSA ($n = 32$)	48.9[b]	Blood	AHI ≥5	Adiponectin, TNF- α	1	B
2008	Li et al. [157]	Thailand	Mild OSA: 22 Moderate OSA: 22 Severe OSA: 24	Non-OSA ($n = 22$)	48.5	Blood EBC	AHI ≥5	8-isoprostane, IL-6, TNF-α, IL-10	1	B
2008	Norman et al. [93]	United states	OSA ($n = 109$)	–	48.5	Blood	Not reported	Serum Aminotransferase	2	B
2008	Petrosyan et al. [150]	Greece	Obese non-OSA ($n = 9$) OSA ($n = 26$)	Non-obese and non-OSA ($n = 10$)	48.4[b]	EBC	AHI >20	nNO, eNO, eCO, LTB4, nitrates, H_2O_2	1	B
2008	Takahashi et al. [106]	Japan	OSA candidates to CPAP ($n = 41/38$ male)	Non-OSA ($n = 12/11$ male)	48.3[b]	Blood	AHI >5	TRX, Adiponectin	1	B
2008	Zamarron et al. [123]	Spain	OSA suspected ($n = 96/96$ male) divided in two groups: OSA OSA with hypertension	–	53.3	Blood	AHI >10	PAI-1	1	C

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Table 2 (*continued*)

Year	Author	Country	Cases[a]	Controls	Age (mean in years)	Type of biomarker	OSA diagnostic criteria at PSG	Biomarker	Classification as a biomarker	Level of evidence
2009	Kim et al. [124]	South Korea	Severe OSA ($n = 40/40$ male)	Non-OSA ($n = 34/34$ male)	44.8[b]	Blood	AHI ≥ 5	Nine proteins: Haptoglobin alpha 2 chain Haptoglobin beta chain Chain B, Alpha-Ferrous-Carbon monoxy (T-state) Apolipoprotein M Complement component 3 precursor Serum paraoxonase Complement factor B Complement C4 precursor Complement component C4a	2	B
2009	Kuramoto et al. [107]	Japan	Without or mild OSA ($n = 35/27$ male) Moderate OSA ($n = 35/26$ male) Severe OSA ($n = 46/43$ male)	–	49.5[b]	Blood	Without or mild OSA: AHI <20	SAA, Brachial-ankle PWV	1	B
2009	Lam et al. [77]	China	AHI <5 ($n = 25/25$ male) AHI ≥ 5 ($n = 69/69$ male)		43.7	Blood Urine	AHI ≥ 5	Urinary catecholamines, cortisol, insulin, glucose, lipids	1(Urinary catecholamines) 2(Cortisol Insulin Glucose lipids)	B
2009	Lederer et al. [94]	United states	OSA ($n = 11/6$ male)	Non-smoking healthy ($n = 10/5$ male)	40.0	Blood	AHI ≥ 5	KL-6	2	C
2009	Li et al. [78]	China	Mild OSA ($n = 22$) Moderate OSA ($n = 22$) Severe OSA ($n = 24$)	Smoker control group ($n = 10$) Non OSA ($n = 22$)	44[b]	Blood EBC	AHI ≥ 5	8-isoprostane, TNF-α, IL-6, IL-10	1 (IL-6, IL-10) 2(8-isoprostane, TNF-α)	
2009	Lui et al. [79]	China	AHI 0-15 ($n = 35/35$ male) AHI 15 to <30 ($n = 32/32$ male) AHI ≥ 30 ($n = 44/44$ male)	–	44.3[b]	Blood	AHI ≥ 5	CRP	1	B
2009	Ting et al. [111]	Taiwan	OSA ($n = 263/56.6\%$ male) divided in four groups: Constant low ($n = 138$) Morning drop ($n = 34$) Constant high ($n = 63$) Morning surge ($n = 28$)	–	44.7	Blood	Not reported	Biochemical markers, SSBP	2	B
2009	Ucar et al. [125]	Turkey	Snoring OSA ($n = 62/48$ male)	Snoring non-OSA ($n = 18/10$ male)	48.9[b]	Blood	AHI ≥ 5	Arterial lactate levels	1	B
2010	Lee et al. [126]	Taiwan	OSA ($n = 65/65$ male)	–	38.2	Blood	AHI ≥ 5	hs-CRP	1	B
2010	Pallayova et al. [95]	United states	Severely obese adults from bariatric surgery ($n = 45/9$ male)	–	36.0	Blood	AHI ≥ 5	Glucose, insulin, selected cytokines, HOMA-IS, HOMA-B	2	B
2010	Steiropoulos et al. [127]	Greece	OSA: ($n = 38/33$ male)	Consecutive non-OSA ($n = 23/17$ male)	44.6[b]	Blood	AHI ≥ 15	TNF-α, Il-6,CRP, fibrinogen levels	1 (TNF-α, Il-6) 3(CRP, fibrinogen levels)	B
2010	Ye et al. [80]	China	Mild ($n = 43/32$ male) Moderate ($n = 39/31$ male) Severe ($n = 45/39$ male)	Non-OSA ($n = 52/37$ male)	45.3[b]	Blood	AIH ≥ 5	DNA, IL-6, MDA	1	B

2011	Akinnusi et al. [96]	United States	Non-smokers OSA ($n = 38/38$ male)	Healthy subjects ($n = 12/12$ male)	50.0[b]	Blood	AHI >5	pLOX-1 circulating apoptotic endothelial cells (CD146+, CD45-, CD31+)	1	B
2011	Cintra et al. [128]	Brazil	OSA ($n = 75/75$ male)	Non-OSA ($n = 75/75$ male)	53.2[b]	Blood	AHI >5	Cysteine, homocysteine	1	B
2011	Jurado-Gamez et al. [130]	Spain	OSA ($n = 46/34$ male)	non-OSA: ($n = 23/15$ male)	35-65 (47.5[b])	Blood	AHI ≥5	IRH, oxidative Stress	2	B
2011	Kohler et al. [153]	Switzerland	Therapeutic CPAP ($n = 20/19$ male) Sub-therapeutic CPAP ($n = 21/21$ male	–	20.5[b]	Blood Urine	Not reported	Urinary catecholamine, lipids, insulin resistance	1 (Urinary catecholamines) 2 (Lipids, insulin resistance)	B
2011	Ladesich et al. [97]	United States	None/Mild OSA ($n = 228/122$ male) Moderate OSA ($n = 70/50$ male) Severe OSA ($n = 52/36$ male)	–	54.0[b]	Blood	None/Mild OSA: AHI 0–14	RBC omega-3 fatty acids	2	B
2011	Pallayova et al. [98]	United States	Morbidly obese ($n = 23$)	–	Older than 21 years old	Blood	AHI ≥5	TNF- α receptor 2	1	B
2011	Zamarron et al. [132]	Spain	OSA ($n = 20/20$ male)	–	33-64 (49.9)	Blood	AHI ≥10	ICAM-1, PAI-1, E-selectin, endothelin-1, vWF	1 (ICAM-1, PAI-1) 3(E-selectin, Endothelin-1, vWF)	B
2012	Duru et al. [133]	Turkey	OSA ($n = 43/25$ male)	Non-OSA ($n = 25/17$ male)	45.5[b]	Blood	AHI ≥ 5	S100B	1	B
2012	Feng et al. [81]	China	OSA ($n = 132/132$ male)	Non-OSA ($n = 108/108$ male)	47.4[b]	Blood	AHI ≥5	Chemerin	1	C
2012	Guven et al. [134]	Turkey	OSA ($n = 47/9$ male)	Non-OSA ($n = 29/5$ male)	52.8[b]	Blood	AHI ≥ 5	hs-CRP	1	B
2012	Hira et al. [129]	India	OSA ($n = 40/36$ male)	Non-OSA ($n = 40/36$ male)	Control group: <40 = 12 40-50 = 16 >50 = 12 Study group: <40 = 10 40-50 = 20 >50 = 10	Blood	AHI ≥ 5	Uric acid	1	C
2012	Jurado-Gamez et al. [135]	Spain	OSA ($n = 68/49$ male) divided in: Mild-moderate desaturation group ($n = 31/22$ male) Severe group ($n = 37/27$ male)		48.0	Blood	AHI ≥ 5	MDA, ICAM-1, IRH,P-selectin	2	B
2012	Lee et al. [136]	South Korea	Mild to moderate OSA ($n = 31$) Severe OSA ($n = 22$)	Non-OSA ($n = 20$)	45.7[b]	Blood	AHI ≥5	OxLDL, GPX, LDL, TAS, SOD, 8-isoprostane, PO-56	3	B
2012	Mancuso et al. [137]	Italy	Mild OSA ($n = 7$) Moderate OSA ($n = 15$) Severe OSA ($n = 19$)	Healthy ($n = 32/18$ male)	54.0[b]	Blood	AHI <15	AOPP, FRAP, GSH	2	C
2012	Papaioannou et al. [112]	UK	Community adults ($n = 22/20$male)	Community adults ($n = 22/17$ male)	46.5[b]	Saliva	Not reported	Melatonin	3	C
2012	Simiakakis et al. [138]	Greece	Consecutive subjects referred to sleep laboratory: ($n = 42/27$ male)	Consecutive subjects referred to sleep laboratory: ($n = 24/12$ male)	46.3[b]	Blood	AHI ≥15	d-ROMs, BAP	2	B
2012	Sokucu et al. [139]	Turkey	Adults referred to sleep laboratory with OSA symptoms ($n = 108/72$ male)	–	49.2	Blood	AHI ≥5	RDW	1	C

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Table 2 (*continued*)

Year	Author	Country	Cases[a]	Controls	Age (mean in years)	Type of biomarker	OSA diagnostic criteria at PSG	Biomarker	Classification as a biomarker	Level of evidence
2012	Svensson et al. [131]	Sweden	AHI <15 ($n = 262$) AHI ≥15 ($n = 136$)		50.0	Blood	AHI ≥15	CRP, TNF-α, IL-6 MPO, lysozyme	3	A
2013	Aihara et al. [108]	Japan	Consecutive OSA ($n = 38/21$ male), none had been previously diagnosed with or treated for OSA divided in: Group sputum + ($n = 28/15$ male) Group sputum − ($n = 10/6$ male)	–	55.4[b]	Blood Sputum	AHI ≥ 5	Leptin, cytokine, albumin	2	B
2013	Chung et al. [140]	Canada	Preoperative patients ($n = 384/289$ male)	–	60.0	Blood	AHI >5	HCO_3	2	B
2013	Cofta et al. [141]	Poland	Mild-OSA-1 ($n = 21$) Moderate-OSA-2 ($n = 18$) Severe-OSA-3 ($n = 21$)	Non-smoking: ol-OSA-0 ($n = 20$)	54.5[b]	Blood	AHI ≥ 5	E-selectin, L-selectin, P-selectin	1	B
2013	Ferrarini et al. [142]	Spain	Non-severe OSA ($n = 15/11$ male) and severe OSA ($n = 18/12$ male)	–	Non-severe: OSA 32–81 years Severe OSA: 34–85 years	Blood	AHI ≥ 5	Glycerophoshoplipids, porphyrins, fatty acyls, amino acid, metabolites and derivates, peptides, PE	2	B
2013	Guo et al. [82]	China	OSA suspected: Mild OSA ($n = 14$) Moderate OSA ($n = 11$) Severe OSA ($n = 29$)	OSA suspected: ($n = 9$)	47.8[b]	Blood	AHI ≥ 5	TRX	1	B
2013	Hirotsu et al. [143]	Brazil	OSA ($n = 339/18.8\%$ male)	non-OSA ($n = 682/25.9\%$ male)	44.6[b]	Blood	AHI ≥ 15	Uric acid	1	A
2013	Kurt et al. [144]	Turkey	Group A ($n = 20$): AHI <5/h Group B ($n = 15$): AHI 5-14 Group C ($n = 26$): AHI 15-29.9 Group D ($n = 37$): AHI ≥30/h	–	52.5[b]	Blood	AHI ≥5	PDW, CRP, MPV, RDW	1 (PDW) 3 (CRP, MPV, RDW)	B
2013	Murase et al. [109]	Japan	Mild OSA ($n = 37/24$ male) Moderate OSA ($n = 24/18$ male) Severe OSA ($n = 26/18$ male)	Non OSA ($n = 15/8$ male)	54.8[b]	Blood	AHI ≥5	Plasma Ngal	2	B
2013	Ntalapascha et al. [145]	Greece	OSA ($n = 18$)	Non-OSA ($n = 13$)	49.5[b]	Blood	AHI >30	GSH, GSSG, 8-isoprostane, TBARS, catalase activity, SOD, TAC	1 (GSH, GSSG) 3(8-isoprostane, TBARS, catalase activity, SOD, TAC)	B
2013	Ozben et al. [146]	Turkey	OSA ($n = 60/33$ male)	Healthy ($n = 23/19$ male)	49.8[b]	Blood	AHI ≥5	Copeptin	3	B
2013	Pinto et al. [154]	Portugal	Mild/moderate OSA ($n = 36$) Severe OSA ($n = 31$)	–	49.5[b]	Blood Urine	RDI ≥5	NOx U-NE levels	1	B
2013	Shi et al. [83]	China	OSA ($n = 126/126$ male)	Non-OSA ($n = 74$)	49.0[b]	Blood	AHI >5	S100A12	1	B
2013	Wang et al. [85]	China	Moderate to severe OSA ($n = 20/18$ male	Non-OSA ($n = 15/14$ male)	38.5[b]	Blood	AHI ≥15	Fractalkine	1	C
2013	Wang et al. [84]	China	OSA ($n = 192/192$ male)	Non-OSA ($n = 144/144$ male)	49.0[b]	Blood	AHI ≥5	Ometin-1	1	B
2013	Zhang et al. [86]	China	Mild OSA ($n = 15/15$ male) Moderate OSA ($n = 24/24$ male) Severe OSA ($n = 36/36$ male)	Non-OSA ($n = 23/23$ male)	32.5[b]	Blood	AHI ≥5	Cystatin C, hsCRP	1	B
2014	Tual-Chalot et al. [147]	France	OSA ($n = 20/20$ male)	Non-OSA ($n = 15/15$ male)	43.3[b]	Blood	AHI ≥5	Circulating microparticles	2	B

2014	Vavougios et al. [148]	Greece	OSA (n = 120/100 male)	–	48	Blood	AHI >5	DJ-1 protein	1	B
2014	Wang et al. [87]	China	OSA (n = 159/98 male)	Healthy (n = 104/64 male)	53.0[b]	Blood	AHI >5	YKL-40	1	B

Abbreviations 8-OHdG = 8-hydroxy-2'-deoxyguanosine, AHI = apnea/hypopnea index, AIC = akaike information criterion, ALT = alanine aminotransferase, AOPP = advanced oxidation protein products, AST = aspartate aminotransferase, BAP = biological anti-oxidant capacity, BMI = body mass index, BP = blood pressure, CK = creatine phosphokinase, CPAP = continuous positive airway pressure, CRP=C-reactive protein, d-ROMs = derivates of reactive oxygen metabolites, DPB = diastolic blood pressure, EBC = exhaled breath condensate, eCO = exhaled carbon monoxide, eNO = exhaled nitric oxide, FFA = free fatty acids, FPG = fasting plasma glucose, FRAP = ferric reducing antioxidant power, GPX = glutathione peroxidase, GSH = reduced glutathione, GSH = total glutathione, GSSG = oxidized glutathione, H_2O_2 = hydrogen peroxide, HCO_3 = bicarbonate, HOMA-B = pancreatic beta-cell function, HOMA-IR = homeostasis model assessment of insulin resistance, HOMA-IS = homeostasis model assessment estimates of insulin sensitivity, hs-CRP = high sensitivity C-reactive protein, ICAM-1 = intercellular adhesion molecule-1, IL-6 = interleukin-6, IL-8 = interleukin-8, IRH = ischemic reactive hyperemia, LDA = linear discriminant analysis, LDL = serum low-density lipoprotein, LH = luteinizing hormone, LTB4 = leukotriene B4, MAP = mean arterial pressure, MCP-1 = monocyte chemoattractant protein-1, MDA = malondialdehyde, MMP-9 = metalloproteinase-9, MPO = myeloperoxidase, MPV = mean platelet volume, MVDA = multivariate data analysis, NE = norepinephrine, NF-kB = proinflamatory transcription nuclear factor, Ngal = neutrophil gelatinase, NME = normetanephrine, nNO = nasal nitric oxide, NOx = reduced plasma nitrate, NSE = neuron-specific enolase, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, oxLDL = oxidized low-density lipoprotein cholesterol, PAI-1 = plasminogen activator inhibitor-1, PDW = platelet distribution width, PE = phosphoethanolamie, pLOX-1 = plasma LOX-1, PRL = prolactin, PSG = polysomnography, PWV = pulse wave velocity, RDI = respiratory disturbance index, RDW = red cell distribution width, SAA = serum amyloid, SBP = systolic blood pressure, slL-R = soluble IL-6 receptor, SOD = superoxide dysmutase, SSBP = post-to pre-overnight sleep systolic blood pressure, sTNFR-1 = soluble tumor necrosis factor- α receptor, TAC = total antioxidant capacity, TAS = total antioxidant status, TBARS = thiobarbituric acid-reactive substances, TNF-α = tumor necrosis factor alpha, TRH = thyroid releasing hormone, TRX = thioredoxin, TSH = thyroid stimulating hormone, U-NE = urinary norepinephrine, UVDA = univariate data analysis, VCAM-1 = vascular cell adhesion molecule-1, VEGF = vascular endothelial growth factor, vWF = von Willebrand factor, WHR = waist-to-hip ratio, WL = weight loss.

[a] All terms that mean obstructive sleep apnea (SDB, SRDB, OSAS) were standardized as OSA.

[b] Mean calculated by author.

Table 3
Potential biomarkers identified in children.

Potential biomarkers	Amount of studies that investigated this biomarker
Insulin	2
8-isoprostane	1
Alpha-amylase	1
Glucose	1
hsCRP	1
Kallikrein-1	1
Lipopolysaccharide-binding Protein	1
Macrophage migration inhibitory factor	1
Orosomucoid-1	1
P-selectin	1
Proteomic patterns	1
Salivary cortisol	1
(n-sCor, m-sCor, sub-sCor, r-sCor)	1
Urinary Neurotransmitters	1
Urocortin-3	1
Uromodulin	1
VOCs mixtures	1

hsCRP = high sensitivity C-reactive protein, m-sCor = morning sCor, n-sCor = night sCor, r-Scor = ratio sCor, sCor = salivary cortisol, sub-sCor = subtraction sCor, VOCs = complex volatile organic compounds.

made, thereby justifying efforts to provide a critical appraisal of this field, and further indicate future research directions that rely on the cumulative evidence presented heretofore [159]. We should emphasize that despite our comprehensive search strategy, 29 studies were found by hand-searching in the reference list, and that the absence of universally agreed upon PSG criteria for the

Table 4
Potential biomarkers identified in adults.

Potential biomarkers	Amount of studies that investigated this biomarker
IL-6	7
TNF-α	5
CRP	4
8-isoprostane, hs-CRP, ICAM-1.	3
Adiponectin,IL-10, IL-8, PAI-1, S100B,	2
TRX, Urinary catecholamines, VEGF, uric acid	
8-OHdG, Arterial lactate levels,	1
Brachial-ankle PWV, Chemerin, CK, Cystatin C, Cysteine, DJ-1, E-selectin, eCO, eNO, Epinephrine, Fractalkine, GSH, GSSG, H2O2, Homocysteine, L-selectin, LTB4, MCP-1, MMP-9, NF-kB, Nitrates, nNO, Noradrenaline, Norepinephrine, NOx, NSE, Ometin-1, P-selectin, PDW, pLOX-1RDW, S100A12, SAA, slL-R, sTNFR-1, TNF-α receptor 2, VCAM-1, YKL-40.	

8-OHdG = 8-hydroxy-2'-deoxyguanosine, CK = creatine phosphokinase, DJ-1 = gene that is involved in tumorigenesis and in maintaining mitochondrial homeostasis, eCO = exhaled carbon monoxide, eNO = exhaled nitric oxide, GSH = reduced glutathione, GSSG = oxidized glutathione, H_2O_2 = hydrogen peroxide, hs-CRP = high sensitivity C-reactive protein, ICAM-1 = intercellular adhesion molecule-1, IL-10 = interleukin-10, IL-8 = interleukin-8, LTB_4 = leukotriene B_4, MCP-1 = monocyte chemoattractant protein-1, MMP-9 = matrix metallopeptidade-9, NF-kB = proinflamatory transcription nuclear factor kappa B, nNO = nasal nitric oxide, NOx = nitrate mono-nitrogen oxides, NSE = neuron-specific enolase, PAI-1 = plasminogen activator inhibitor-1, PDW = platelet distribution width, pLOX-1 = plasma lectin-like oxidized low-density lipoprotein receptor-1, PWV = pulse wave velocity, RDW = red cell distribution width, SAA = serum amyloid, S100B=S100 calcium binding protein B, slL-6R = soluble interleukin-6 receptor, sTNFR-1 = soluble tumor necrosis factor receptor-1, TNF-α rR2 = tumor necrosis factor alpha receptor 2, TRX = thioredoxin, VCAM-1 = vascular cell adhesion molecule-1, VEGF = vascular endothelial growth factor, YKL-40 = human cartilage glycoprotein-40.

diagnosis of OSA along with the systematic inclusion of patient referral populations may further alter any conclusions pertaining to the validity of a proposed set of promising biomarkers. Notwithstanding such concerns, the cumulative data support the concept that biological markers should provide valid tools to identify OSA in both children and adults, even if a specific set of biomarkers cannot be firmly recommended at this preliminary stage of discovery and validation.

Conclusions

The majority of pediatric studies have been performed in the USA and Greece, while adult studies were primarily conducted in China, USA and Japan. Most of studies used blood biomarkers. Studies in adults primarily explored the investigation of IL-6, TNF-α, and hsCRP as potentially promising biomarkers. There was not a specific biomarker that was tested by a majority of authors in pediatric studies, i.e., each paper evaluated different non-overlapping types of biomarkers.

Only the combination of kallikrein-1, uromodulin, urocortin-3 and orosomucoid-1 appears to provide sufficient accuracy to be considered a potential OSA diagnostic test in children. In adults, IL-6 and IL-10 appear to exhibit a favorable profile as biomarkers aiming to discriminate patients with and without OSA.

Practice points

The present scoping review shows that:

1) Although there are a substantial number of studies published in the literature, most of the explored approaches do not identify definitive biomarkers.
2) The combination of kallikrein-1, uromodulin, urocortin-3 and orosomucoid-1 appears to have sufficient accuracy to be considered an OSA diagnostic test in children.
3) IL-6 and IL-10 exhibit favorable potential to become a good biomarker to identify OSA and non-OSA adults.

Research agenda

In the future we need to:

1) Improve the reporting methodology by calculating and reporting sensitivity and specificity, using samples from community, and employing a definitive AHI cut-off value for PSG-based diagnosis of OSA.
2) Prepare systematic review and meta-analysis to critically evaluate the diagnostic value of biomarkers in OSA diagnosis.
3) Estimate cost-effectiveness of biomarkers tests.
4) Formulate potential future exploratory research directions and unbiased discovery approaches aiming at advancing this promising area.

Conflicts of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2014.11.004.

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